

# Enrolling Minors in COVID-19 Vaccine Trials

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It is widely agreed that an effective response to the coronavirus disease 2019 pandemic needs to include a vaccine that is safe and effective for minors. However, many current vaccine trials have no plans for when to enroll minors. Others have recently proposed enrolling minors as young as 12 years old. This lack of a systematic approach raises 2 concerns. Waiting too long to enroll minors could unjustly deny minors and their families the benefits of a vaccine and has the potential to delay an effective response to the pandemic by a year or longer. At the same time, enrolling minors too soon runs the risk of exposing them to excessive risks. With these concerns in mind, in the present article, we propose recommendations for when and how to enroll minors in vaccine trials for the coronavirus disease 2019.

An effective response to the coronavirus disease 2019 (COVID-19) pandemic requires a vaccine that is safe and effective for all populations, including minors. However, many sponsors do not have plans for when to enroll minors. More recently, some have proposed expanding enrollment to include minors, in one case enrolling children as young as 12 years old.<sup>1</sup> Enrolling minors too soon runs the risk of exposing them to excessive research risks. Yet, waiting too long could unjustly deny minors and their families the benefits of a vaccine and has the potential to delay an effective response to the pandemic by a year or longer. Researchers and sponsors thus need systematic guidance on when and how to enroll minors in vaccine trials for COVID-19 in ways that are consistent with regulatory guidelines and ethical norms.<sup>2-4</sup>

## COVID-19 IN MINORS

Research conducted early in the COVID-19 pandemic revealed that few minors were being infected.<sup>5</sup> More recent data

suggest minors are becoming infected in increasing numbers. As of November 12, 2020, >1 000 000 minors, constituting 11.5% of all COVID-19 cases, have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) in the United States.<sup>6</sup> Most infected children are asymptomatic or have only mild symptoms. However, minors, especially those from racial and ethnic minority groups, as well as minors with underlying health conditions and disabilities, can become seriously ill, with some experiencing multisystem inflammatory syndrome in children (MIS-C), a condition associated with symptoms ranging from severe abdominal pain to organ damage.<sup>7</sup> Of the >1 000 000 minors known to have been infected with SARS CoV-2 in the United States, there have been >1000 cases of MIS-C and 138 deaths.<sup>8,9</sup> By way of comparison, 188 minors in the United States died during the most recent influenza season, a disease burden considered high enough to justify routine seasonal influenza vaccination for children.<sup>10</sup>

## abstract



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The COVID-19 pandemic has also resulted in significant social and personal harm for minors. The closure of many schools and day care centers has resulted in minors attending classes online, which denies school-aged children the educational and social benefits of in-person interactions with teachers and peers and the food, safety, and care which school affords many children. Moreover, online learning likely disadvantages minors from low-income groups who do not have access to the technology and space needed for electronic learning at home. More generally, the pandemic has dramatically interfered with and undermined children's ability to pursue activities integral to healthy development.<sup>11</sup>

As businesses reopen but children continue to attend school from home, parents and guardians for whom child care is unaffordable face difficult trade-offs between working and caring for their children. Finally, although few minors develop significant disease, they can transmit the infection to others.<sup>12</sup> A safe and effective vaccine would thus offer significant benefits to minors, their families, and society generally.

### **MINORS AND VACCINE TRIALS**

Most minors are not able to understand and provide their own informed consent. As a result, minors are less able to protect themselves from being exposed to excessive research risks. To address this concern, enrollment of minors in clinical trials requires the permission of the minors' parents or legal guardians along with the assent of minors who are capable of providing it. In addition, minors should be enrolled only when the trial poses low risks or offers a potential for participant benefit that justifies the risks.

A common way to satisfy these requirements is to enroll minors only

after there is evidence of safety and efficacy in adults, which may include evidence of immunogenicity in the case of vaccines.<sup>2</sup> By ensuring that there is evidence of safety and a potential for benefit before enrolling minors, this approach offers one way to protect minors from being exposed to excessive research risks.

Yet, waiting until safety and efficacy have been established in adults could substantially delay an effective pandemic response. This delay also postpones the health, social, and psychological benefits that access to a vaccine could provide children and their families, an especially significant loss when there are only limited options for treating COVID-19. Although children can reduce their risks by practicing distancing, wearing masks, and avoiding group settings, these practices pose social costs to children and their families. Moreover, it is difficult to monitor minors, especially adolescents and older children, to ensure they follow these practices consistently.

The costs that delay poses to children, their families, and society provide strong reasons to consider enrolling minors in vaccine trials for COVID-19 before safety and efficacy have been established in adults. Is it possible to do this ethically?

### **EXPEDITED ENROLLMENT OF MINORS IN SARS COV-2 VACCINE TRIALS**

Enrolling children in vaccine trials at the outset, before establishing safety or efficacy in adults, would minimize the delay in assessing vaccines in minors. However, enrolling children before there is evidence that the vaccine being tested is safe or effective has the potential to expose them to excessive risks. A different way to address this concern is to enroll minors after there are sufficient safety data in adults, but before there is evidence of efficacy (Table 1).

To pursue this strategy, enrollment of minors should begin with those who are most similar to the adults from whom safety data were collected, with particular attention to populations that were excluded or otherwise not enrolled in the adult trials. This typically will involve enrolling older adolescents who are most similar to adults physiologically. Data suggest that older adolescents have a capacity to understand clinical trials similar to that of average adults.<sup>13</sup> Hence, beginning with older children, and requiring their assent, along with the permission of their parents, provides strong protection against their being exposed to excessive risks. This suggests that, once there are sufficient safety data in adults, enrolling older adolescents can be ethically appropriate.

To further minimize risks, enrollment should begin with a small number of older and healthy adolescents. If no safety concerns are identified in this subgroup, the trial should proceed to a larger group of older adolescents and then repeat this approach with healthy younger adolescents. The ethically most challenging groups, young children who cannot understand and minors with health conditions that put them at increased risk for COVID-19 complications, should not be enrolled until there are sufficient safety data in adolescents. If safety concerns are identified in adolescents, these groups should not be enrolled until there is evidence of efficacy that justifies the risks.

### **PRIORITIZING CANDIDATES FOR PEDIATRIC TRIALS**

More than 180 vaccine candidates are currently in development,<sup>14</sup> with at least 12 in phase 3 trials.<sup>15</sup> Early testing of all these vaccine candidates in children could expose large numbers of minors to risks. Careful planning, coordination, and prioritization can help mitigate these risks and minimize the potential for

**TABLE 1** When to Enroll Minors in Vaccine Trials for COVID-19

| Approach | Description                                | Advantages  | Disadvantages  |
|----------|--|---|--|
| Standard | After safety and efficacy in adults        | Minimizes risks to participants<br>Ensures some potential for participant benefit<br>Approvable under regulations<br>Protects public trust                                  | May significantly delay effective response to pandemic<br>Delays vaccine for children and families   |
| Earlier  | After safety but before efficacy in adults | Reduces risks to participants<br>Reduces time to effective response to pandemic<br>Reduces time to vaccine for children and families<br>Likely approvable under regulations | Exposes participants to risks without potential benefit<br>Potential loss of public trust if participants harmed   |
| Earliest | Before safety or efficacy in adults        | Minimizes time to effective response to pandemic<br>Minimizes time to vaccine for children and families   | May expose participants to excessive risks<br>Likely not approvable under regulations<br>Increased potential for loss of public trust if participants harmed |

public distrust if pediatric research participants are harmed.

Given the relatively low risks of serious harm that they face from COVID-19, children should not be enrolled until there is sufficient evidence that the vaccine candidate poses low risks. At the same time, the possibility that pediatricians might administer the vaccine to minors off-label suggests that waiting until the vaccine has been approved and marketed for adults may make it difficult to enroll sufficient numbers of minors. This possibility underscores the importance of planning for the recruitment of minors prospectively and being prepared to enroll them once there are sufficient safety data in adults, rather than waiting for approval and marketing in adults. One possibility would be to consider convening an early meeting of the Data and Safety Monitoring Board to assess whether there is sufficient evidence of safety to recommend that the enrollment of minors should begin.

If many vaccine candidates demonstrate sufficient safety data, additional criteria can be used to prioritize candidates for testing in minors, including the following: (1) evidence of efficacy and/or likelihood of earlier licensure; (2) public health considerations, such as cost or absence of storage

requirements that might hinder wide distribution; and (3) ease of administration in children.<sup>16</sup> For example, Pfizer recently announced that, at the first interim analysis, its vaccine candidate was found to be 95% effective.<sup>17</sup> A week later, Moderna announced that, at the first interim analysis, its vaccine candidate was found to be 94.5% effective.<sup>18</sup> If confirmed, these findings would provide strong grounds for prioritizing these vaccines for testing in minors. The Pfizer vaccine must be stored at low temperatures (−80°C) until several days before administration. This requirement will reduce its availability in many parts of the world and would provide a reason against prioritizing this vaccine candidate for testing in minors if other vaccine candidates are found to have similar efficacy and pose fewer logistic challenges.

**IS INSTITUTIONAL REVIEW BOARD APPROVAL FEASIBLE?**

US research regulations permit institutional review boards to approve enrollment of children in 3 categories of clinical trials: (1) minimal risk, (2) prospect of direct benefit, and (3) minor increase over minimal risk. Without evidence of safety or efficacy, administration of experimental interventions poses

more than a minor increase over minimal risk and does not offer a potential for benefit. Trials of experimental vaccine candidates thus typically are not approvable by institutional review boards in minors from the outset. However, vaccine trials, unlike many other clinical trials, frequently enroll tens of thousands of adults. For example, the Pfizer and Moderna phase 3 trials have enrolled >43 000 and 30 000 participants respectively.<sup>18,19</sup> Assuming that half the participants received 2 doses of the vaccine candidate, a strong safety record in this many adults could provide grounds for categorizing a trial as minimal risk in older adolescents. The fact that a vaccine candidate uses a platform with a record of safety in children would provide additional support for this determination.<sup>20</sup> In contrast, the fact that there is limited experience with a particular type of vaccine, such as the novel mRNA vaccines being tested by Pfizer and Moderna, may provide reason to collect more safety data before concluding that they pose acceptable risks in minors.

Next, a finding that a vaccine candidate has met its efficacy end point at an interim analysis in adults, as occurred in the Pfizer and Moderna trials, would provide strong support

for categorizing the trial as prospect of benefit in minors. In contrast, the potential benefits to children of an experimental vaccine that has not yet been found effective will be modest. Still, a strong safety record in adults, even one that is not sufficient to support a determination of minimal risk, likely supports a finding of low risk in adolescents, which could be justified by a modest chance of benefit.

Finally, to be approved as minor increase over minimal risk, the trial must have the potential to yield generalizable knowledge about the subjects' disorder or condition. For this purpose, it has been argued that being at risk for a particular disease qualifies as having a condition.<sup>21</sup> Trials of vaccine candidates will yield generalizable knowledge about the condition of being at risk for COVID-19. Hence, when the safety record is not strong enough to justify a finding of minimal risk, it may be possible to approve the trial as minor increase over minimal risk.

These considerations suggest that, once there is evidence of safety in adults, enrollment of minors is likely to be approvable for many trials, especially if they start with older, healthy adolescents.

## COMMUNITY PARTNERSHIPS

Forming community partnerships can help to ensure that pediatric vaccine trial participants reflect the geographic and demographic diversity of the populations affected by the pandemic. Such partnerships could also help recruitment, ensure that any community concerns are addressed, and facilitate a fair process of selection when there are more interested participants than participant slots. Equally important, these partnerships can aid in garnering public trust in the research process, making it more likely that individuals will use an effective COVID-19 vaccine.<sup>22</sup>

## ASSESSING FOR SERIOUS COMPLICATIONS

Rare and delayed side effects, such as the possibility of MIS-C, are unlikely to emerge during clinical trials. Hence, postmarketing surveillance should include prolonged monitoring. Finally, plans should be in place for medical care for pediatric participants who experience adverse events.

## CONCLUSIONS

A systematic approach is needed for determining when and how to enroll

minors in vaccine trials for COVID-19. Enrolling minors, beginning with older, healthy adolescents, after there is sufficient evidence of safety in adults, addresses concerns about exposing children to excessive research risks, and doing so before efficacy has been demonstrated in adults can speed up the process of providing access to a safe and effective vaccine for children and their families, thereby reducing the time until the pandemic is effectively addressed.

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## ABBREVIATIONS

COVID-19: coronavirus disease 2019  
MIS-C: multisystem inflammatory syndrome in children  
SARS CoV-2: severe acute respiratory syndrome coronavirus 2

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